Cystic Renal Tumors: New Entities and Novel Concepts
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- Differential diagnosis of renal tumors with cysts
- Novel entities of cystic renal tumors
- VHL gene alterations and cyst formation
- A model for cystic and non-cystic tumorigenesis of clear cell carcinoma

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Overall, cystic change occurs in up to 15% of RCCs. Cystic renal tumors are not classified as separate pathologic entities. Renal tumor entities with characteristic cysts include:

- Cystic Nephroma / Mixed Epithelial and Stromal Tumor
- Tubulocystic carcinoma
- Synovial sarcoma („Cystic embryonal sarcoma“)
- Acquired Cystic Disease-associated Renal Cell Carcinoma
- Clear cell renal cell carcinoma with prominent cysts
- Multilocular cystic renal cell carcinoma

MIXED EPITHELIAL AND STROMAL TUMOR/CYSTIC NEPHROMA
In 1993, Pawade et al. described three cases of a novel cystic renal tumor which they termed “cystic hamartoma of the renal pelvis.” Additional cases have been reported as “mesoblastic nephroma of adults” and as “mixed epithelial and stromal tumor of the kidney.” The last terminology is preferred since these tumors clearly have no relationship to mesoblastic nephroma of infants and since they appear to be mixtures of neoplastic epithelial components and spindle cells. There is a strong predominance of women, often of perimenopausal age. Most of these tumors appear to arise centrally in the kidney and to grow as expansile masses. The tumors lack a thick fibrous wall but compressed renal tissue usually forms a pseudocapsule in the larger tumors. The tumors are grossly composed of multiple cysts and solid areas. The solid areas may be extensive. The septa of the cysts are thicker than is typical of cystic nephroma, cystic partially differentiated nephroblastoma, and multilocular cystic clear cell renal cell carcinoma. These are complex tumors composed of large cysts, microcysts, and tubules. The largest cysts are lined by columnar and cuboidal epithelium which sometimes forms small papillary tufts. The microcysts and tubules are lined by flattened, cuboidal, or columnar cells. The stroma consists of a variably cellular population of spindle cells with plump nuclei and abundant cytoplasm. Areas of myxoid stroma and fascicles of smooth muscle cells may be prominent. Blood vessels with thick walls may be present. Fat cells may be
present. Mitotic figures and atypical nuclei have not been reported. The relationship between cystic nephroma and mixed epithelial and stromal tumor of the kidney has been controversially discussed. Recently, the term Renal Epithelial and Stromal Tumor (REST) has been proposed as a unifying term of Cystic Nephroma and Mixed Epithelial and Stromal Tumor.

References

Tubulocystic Renal Cell Carcinoma
Tubulocystic Carcinoma of the Kidney is a recently described tumor entity which was not included in the 2004 WHO classification. The tumors were originally thought to represent low grade collecting duct carcinomas. Recently, a large series of 31 cases have been published. (Amin et al.). In the published series, men have predominated. Follow up data are limited but only two patient has been reported to have had metastasis. The tumors have ranged from 2 mm to 85 mm in diameter. Tubulocystic carcinoma has a distinctive gross appearance: well-circumscribed with an off-white cut spongy surface which shows innumerable cysts filled with clear fluid. The cyst lining is smooth and the cysts are fairly uniform in size, compared to the highly variable sizes of the cysts of clear cell renal cell carcinoma.Tubulocystic carcinoma is seen microscopically to be composed of cysts of variable size ranging down to ones of the diameter of a cross section of a renal tubule. The cysts are lined by a single layer of carcinoma cells with eosinophilic cytoplasm. The contours of these cells varies from cuboidal to hobnail or flattened. The nuclei are spherical and nucleoli are usually prominent in many of the nuclei. Necrosis and mitotic figures are rare. The septa between the cysts are thin and composed of fibrous tissue. Immunohistochemically, Azoulay et al. found 11 of 11 tumors to react with antibody to CD10. Yang et al. found 7 of 8 to react focally or weakly with antibody to cytokeratin 7.

References
Primary renal synovial sarcomas

Synovial sarcoma of the kidney is an entity which is characterized by a specific morphology and specific cytogenetic characteristics. They consist of spindle cells and frequently have large cysts. Many cases show local recurrence after nephrectomy. Most cases are diagnosed between the ages of 20 and 50 years. Microscopically, tumors are characterized by monomorphic plump spindle cells. The cysts are lined by mitotically inactive epithelial cells without striking cellular atypia. The tumors have been previously described as embryonal sarcoma of the kidney. There is a slight male predilection (1.6:1). No bilateral tumors were identified yet. The spindle cells are immunoreactive for EMA, CD56 and sometimes for CD99. They are non-reactive for desmin, actin, S100 and cytokeratins. The cyst epithelium is cytokeratin-positive. Synovial sarcoma is cytogenetically characterized by the translocation t(X;18)(p11.2/q11.2), generating a fusion between the SYT-gene on chromosome 18 and one member of the SSX family gene (SSX1;SSX2; SSX4) on chromosome X. Molecularly confirmed primary synovial sarcomas of the kidney have demonstrated the characteristic SYT-SSX gene fusion. In contrast to soft tissue synovial sarcoma where the SYT-SSX gene fusion is more common than the alternative SYT-SSX2 form, the majority of renal synovial sarcomas have so far demonstrated the SYT-SSX2 gene fusion. There is a tendency for a predominance of monophasic spindle morphology of these tumors in the kidney and there are more rarely biphasic tumors. Although prognostic data are limited, there are case reports describing tumors which have responded to chemotherapy. However, recurrence is common.

References
Acquired Cystic Disease-associated Renal Cell Carcinoma
This recently described RCC is associated with end-stage kidneys with acquired cystic disease. Long-term renal dialysis has long been known to predispose to the development of acquired cystic disease and renal cell neoplasms. Many of these appear to be typical clear cell, papillary, and chromophobe renal cell carcinomas. However, morphologically distinctive carcinoma has been discovered in patients with acquired cystic disease. Some appear to be unique to end-stage renal disease and acquired cystic disease. The kidneys are atrophic and have numerous cysts, typical of acquired cystic disease. The carcinomas are usually well-circumscribed and the larger ones often have a thick fibrous pseudocapsule which often contains foci of calcification. More than half the tumors appear to arise in a cyst. The architecture is complex with acinar, compact sheets, microscopic and macroscopic cysts in various combinations. Papillar structure ranging from very focal to more than 50% of the tumor, are present in roughly half the tumors. Oxalate crystals are frequent. In the study by Tickoo et al 1 patient died of widespread metastases and 2 other patients had lymph node metastases at the time of nephrectomy.

References

Clear cell renal cell carcinoma with prominent cysts / Multilocular cystic renal cell carcinoma
In less than 5% of clear cell RCCs, multiple cysts are predominant. Such tumors are well circumscribed, with non-communicating cysts separated by irregular, thick fibrous septa, reminiscent of a multilocular cyst. These so-called cystic or multilocular cystic RCCs are considered a subtype of clear cell RCC. The lining epithelium of the cysts is often attenuated or even absent, but the structures do not represent cystic degeneration of a clear cell RCC of the usual type. Multilocular cystic RCCs are distinguished from multilocular cysts by the presence of nodular aggregates of clear cells, in at least some portion of the cyst wall. The identification of small aggregates of low-grade clear cells in the wall of the cysts is important for the correct diagnosis. If a stringent definition of multilocular cystic RCCs is applied, malignant behavior of these tumors has not been reported. Multilocular cystic RCCs must be distinguished from RCCs with cystic changes. The latter have expansile clear cell masses in their cyst walls.

References

The Function of the VHL protein in renal cancer: a new progression model for VHL-associated RCC via cyst-dependent and cyst-independent pathways

Between 24-45% of VHL patients develop clear cell renal cell carcinoma (ccRCC). Inactivating germline mutations of the VHL gene represents the genetic hallmark of this syndrome and have been demonstrated in almost all VHL patients. Sporadic clear cell RCC is characterized by inactivation of the VHL gene by deletion, mutation or promoter hypermethylation in about 70% of the tumors.

The functions of the VHL protein (pVHL) have been extensively studied in the last 15 years. The VHL protein (pVHL) is implicated in cell-cycle control and gene regulation, and requires transcription-dependent nuclear-cytoplasmic trafficking for its function. There are two biologically active VHL protein isoforms: pVHL(30) and pVHL(19). The distribution of VHL protein isoforms varies in the nuclear and cytoplasmic compartments of renal tumors and alteration of subcellular pVHL trafficking is of potential relevance for the biological behavior of clear-cell RCC. The pVHL functions as a recognition subunit in a E3 ubiquitin protein ligase complex, targeting the hypoxia-inducible transcription factor a (HIF-a) for ubiquitin mediated degradation in the presence of oxygen. Loss of VHL function causes accumulation of HIF-1 subunits in the cytoplasm and their translocation to the nucleus. Loss of VHL function results in strongly enhanced transcription of HIF-a inducible genes, especially in up-regulation of CXCR4. Therefore, the von Hippel-Lindau (VHL) tumor suppressor gene product is one of the major regulators of CXCR4 expression and increased CXCR4 expression levels are most likely a consequence of impaired VHL function in ccRCC. Other pVHL functions include fibronectin matrix assembly, p53 stabilization and transactivation. In addition, pVHL has the ability to bind and stabilize
microtubules by protecting them from depolymerization, which is a prerequisite for cillum formation. Recent evidence highlights a key role for pVHL in the maintenance of the structure of the primary cillum, a microtubule-based cellular sensory organ that inhibits uncontrolled epithelial cell proliferation and cillum formation in the kidney. In fact, two previous in vitro studies showed that by re-expressing pVHL in VHL null ccRCC cell lines pVHL regulates the formation of primary cilia. These observations strongly suggest that loss of VHL function in renal epithelial cells leads to degeneration of primary cilia, which represents a critical step towards cillum formation and ccRCC development in VHL patients. Interestingly, renal cysts are present in about 60% of individuals suffering from the von Hippel-Lindau (VHL) disease.

One might hypothesize that cillum formation is one of the first visible renal alterations in VHL-caused tumor formation. The formation of kidney cysts is a clinical feature of the VHL cancer syndrome and, in at least some cases, is considered a precursor lesion of clear cell RCC. VHL inactivation might be the driving force for the development of kidney cysts that arise in patients with inherited VHL mutations. These new findings draw attention to a primary cillum maintenance network as a new territory for pVHL tumor suppressive activity and have implications for understanding the development of kidney pathology in the setting of VHL disease. On the basis of these findings, a new progression model for VHL-associated CC RCC via cyst-dependent and cyst-independent pathways has been proposed.

References: